36. The method of treating a mammal as claimed in claim 33, wherein the patient is human.

37. The antivenin composition as claimed in claim 27, wherein an antibody source for the F(ab) is polyvalent IgG(T).

38. The antivenin composition as claimed in claim 29, wherein an antibody source for the F(ab) is polyvalent IgG(T).

39. The antivenin composition as claimed in claim 27, wherein the IgG(T) molecules are polyvalent IgG(T).--

REMARKS

Applicants have cancelled claims 20-26 and 28, without prejudice or disclaimer, and have added new claims 31-39. The pending claims are 27 and 29-39. Claims 31-36 are supported in the specification at least at page 23 and claims 37-39 are supported at least at page 16.

In the Office Action mailed March 23, 1993, the Examiner objected to the Abstract of the Disclosure because it was not contained on a separate sheet. As requested, applicants are enclosing a copy of the Abstract on a separate sheet of paper.

The Examiner also requests that the applicant update the status of the parent cases of the instant application. It is believed that the applicants have previously fulfilled this request by the amendment to the specification as indicated at paragraph 7 of the Rule 62 continuation application filed September 22, 1993. If this assumption is incorrect applicants respectfully request further clarification from the Examiner.

At paragraph 18, the Examiner objected to the specification and rejected claims 20-30 under 35 U.S.C. § 112, first paragraph,

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

as allegedly failing to provide an adequate description of the invention and failing to adequately make and/or use the invention, i.e., failing to provide an enabling disclosure. Applicants respectfully traverse this rejection.

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The Examiner has failed to do so.

The specification discloses the manner of making and using the instantly claimed invention by providing: 1) methods for obtaining F(ab) fragments (pages 12-13), 2) a method or disclosure for an antigen-polyacrylamide or alternative type of purification column (pages 6-7 and 13-15), 3) means of determining the characteristics of the F(ab) fragments obtained, including analysis by immunoelectrophoresis (pages 15-17 and Figures 2, 3, 7 and 8) and 4) a means of determining the effectiveness of the antivenin composition against envenomation (pages 18-22) by animal testing.

Specifically, at paragraph 18(A) the Examiner states that "[a]pplicant has not disclosed the claimed antivenin composition as useable for human administration." Applicants respectfully

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

disagree and draw the Examiner's attention to the specification at page 23, lines 1-3, where it is stated:

> The above data indicates that the F(ab) fragments as well as IgG prepared by the processes of this invention can be used in the treatment of human snake bite victims.

Applicant further states at the bottom of the same page that:

> Hence anaphylaxis in individual sensitive to horse serum and serum sickness reactions in general should be significantly reduced by use of these antivenins.

Therefore, applicants have indeed disclosed that the claimed antivenin composition can be usable for human administration.

To more clearly point out and claim the subject matter of the instantly claimed invention, applicants have also added new claims 31-36, which are drawn to the treatment of mammals in need of administration of an antivenin. These claims are supported at least at page 23 of the specification. The undersigned will also submit, when it is obtained from the applicants, a declaration from Dr. Damon Smith under 37 C.F.R. § 1.132, which further supports those claims.

Claims 27 and 29-30 are drawn to an antivenin composition with demonstrated usefulness evidenced in the Specification at pages 18-23. Protection of mice against lethality from a snake venom was demonstrated, and these results are supportive of the usefulness of the claimed composition.

The § 112, first paragraph, rejection concerning "how to use" the invention is overcome by the animal tests alone; however, Dr. Smith's declaration will further support applicants' position. Additionally, the § 112 requirement has been met

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

because a utility under § 101 is established using animal tests. These same tests should readily satisfy the "how to use" requirement under § 112, first paragraph.

The courts have clearly stated that animal tests or even *in vitro* testing can be used to establish patentability of a claimed invention under 35 U.S.C. § 101. In re Jolles, 628 F.2d 1322, 1327 (C.C.P.A. 1980), In re Bergel, 292 F.2d 955, 957 (C.C.P.A. 1961), Cross v. Iizuka, 224 U.S.P.Q. 739, 748 (C.A.F.C. 1985). If these tests are sufficient to demonstrate utility of the instantly claimed invention under the requirements of § 101, such a test should be more than adequate to fulfill the "how to use" requirement under § 112. Applicants contend that the Examiner has in effect acknowledged utility of the claimed invention under § 101 since no rejection under that section of the statute has been made. Therefore, at least one mode of using the instantly claimed invention has been established and the "how to use" requirement under § 112, first paragraph is met. As stated by The Federal Circuit Court:

> The enablement requirement is met if the description enables any mode of making and using the claimed invention.

Engel Indus. Inc. v. Lockformer Co. 20 U.S.P.Q.2d 1300, 1304 (Fed. Cir. 1991). (Emphasis added.)

Original claims 27, 29 and 30, and new claims 37-39 are drawn to an antivenin composition. Appropriate teachings within the specification fully enable one of skill in the art to make and use this composition. Therefore, the claims meet the requirements of § 112, first paragraph.

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

Further, the Examiner's concerns related to either possible toxicity from contaminants during purification or anaphylaxis problems as recited in paragraph 18A are not pertinent to a rejection under § 112, first paragraph. Whether or not there would be contaminants in the preparation or the possibility of anaphylaxis (though applicants do not acknowledge that either is the case), this does not diminish the fact that applicants have enabled the instantly claimed invention. Applicants have provided sufficient information such that one of skill in the art could readily make and use, without undue experimentation, the instantly claimed invention. In any event, the undersigned will also submit a declaration, as soon as it is received from the applicants, which will further indicate that allergic reactions are minimal. Therefore, applicants have met the requirements of § 112, first paragraph.

The rejection as presented at paragraph 18(B) is moot since applicants have cancelled claims related to $F(ab)_2$. Cancellation of these claims does not represent an acquiescence to this rejection.

At paragraph 18(C), the Examiner contends that the applicants have not "sufficiently disclosed the purity of the purified IgG molecules or fragments purified using the instant invention." The Examiner then elaborates further, referring to the possibility of contamination of the purified fragments. Applicants contend that these statements are not dispositive of enablement under § 112, first paragraph. Applicants have demonstrated how to make and/or use the compositions of the

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

pending claims and therefore meet the requirements of § 112, first paragraph.

The immunoelectrophoresis procedure is used to demonstrate that digestion of the IgG molecule has occurred, i.e., that native immunoglobulin bands have disappeared to be replaced by F(ab) or $F(ab)'_2$ bands with accompanying Fc. Failure to indicate the degree of purity, or the presence or absence of contaminating fragments, would not result in failure to enable the invention. Applicants need only show that they have enabled the making and using of the instantly claimed invention. As discussed above, this has been done. Therefore, the Examiner's contention in paragraph 18(C) that the specification is not enabled because "the purity of said antibodies or fragments thereof has not been determined using state of the art techniques" is incorrect. Based on the above amendments and arguments, applicants request reconsideration of the pending claims and withdrawal of the § 112, first paragraph, rejection.

At paragraph 20, the Examiner rejected claim 29 under 35 U.S.C. § 112, first paragraph, alleging that the disclosure is enabling only for claims limited to an antivenin composition which specifically binds venom of the Crotalus genus. Specifically, the Examiner contends that applicants have not described in the specification an antivenin against a toxin other than Crotalus venom, and cites M.P.E.P. §§ 706.3(n) and 706.03(z). Applicants respectfully traverse this rejection.

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

Applicants contend that neither of these sections of the M.P.E.P. is relevant to the alleged rejection. The second paragraph of the M.P.E.P. § 706.03(n) states in part:

> In chemical cases, a claim may be so broad as not be supported by disclosure, in which case it is rejected as unwarranted by the disclosure. If averments in a claim do not correspond to the averments or disclosure in the specification, a rejection on the ground of inaccuracy may be in order. It must be kept in mind that an original claim is part of the disclosure and might adequately set forth subject matter which is completely absent from the specification. ... Whenever an objection or rejection is made on the basis of an incomplete disclosure, the examiner should in the interest of expeditious prosecution call attention to 37 CFR 1.118.

(Emphasis added). Applicants contend that for at least two reasons this section of the M.P.E.P. does not support the rejection. First, the claimed invention is not part of a classical chemical case, and second, the Examiner has not made a rejection based on the ground of inaccuracy.

Section 706.03(z) refers to undue breadth. The second paragraph of this section states:

> However, in applications directed to inventions and arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims.

This section of the M.P.E.P. refers to disclosure involving claims drawn to chemicals and chemical compounds which differ radically in their properties. This analysis is not relevant to the instant claims, since these claims are drawn to "an antivenin composition" and not to chemicals and chemical compounds which differ "radically" in their properties. Antivenin compositions are

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

expected to have at least one property in common, i.e, the ability to neutralize the venom against which the antivenin was made. Therefore, the application of §§ 706.3(n) and 706.3(2) is incorrect.

Furthermore, contrary to the Examiner's assertions, applicants are not required to provide data showing the operativeness of this invention with other antivenin compositions. Instead, "the initial burden is upon the Patent Office to set forth reasonable grounds in support of its position that an applicant's claim may read on inoperative subject matter and not upon the applicant to show that it does not." In re Stark, 172 U.S.P.Q. 402, 406 n.4, (C.C.P.A. 1971). To require applicants to test the operativeness of their invention with every type of antivenin would require a prohibitively large number of examples:

> More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed.

In re Angstadt and Griffin, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Moreover, there is no "magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling' and sets forth the 'best mode contemplated'", at the time the application was filed, In re Borkowski, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Moreover, a specification need not

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

contain even a single working example, Borkowski, 164 U.S.P.Q. at 645.

Applying the foregoing legal standard, applicants' specification is fully enabling. Although the antivenin mentioned in the Office Action may represent a preferred embodiment of the present invention, the invention is not limited to that antivenin. Applicants' specification clearly discloses the starting materials, a protocol for manufacturing the desired antivenin, and a protocol for testing the effectiveness of the antivenin. One of ordinary skill in the art can readily obtain, without undue experimentation, the instantly claimed invention.

Without acquiescing in the propriety of the rejection, and solely to expedite prosecution, the undersigned will submit when received from applicants a declaration, which describes the use of F(ab) fragments to Vipera bera toxin. Thus, in addition to the Crotalus antivenin, applicants will provide a second example of an antivenin made from F(ab) fragments. Accordingly, the § 112, second paragraph, rejection should be withdrawn.

In paragraph 21, the Examiner rejected claims 20-30 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully traverse this rejection.

Claims 20-26 and 28 have been cancelled without prejudice or disclaimer; therefore, the rejection as it pertains to these claims is moot. The Examiner contends that claims 27-30 are indefinite in the recitation of "active against." Applicants

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

have amended claims 27 and 30 to recite "specifically binds," which the Examiner has suggested as a preferred substitution.

In paragraph 21 of the Office Action, the Examiner also stated that claims 27-29 are indefinite in "the recitation of produce an electrophoresis because it is unclear what this means" and "in the recitation of showing that anti-$F(ab)_2$ materials give a precipitation band against F(ab) fragments but produce no precipitation band against anti-F(c) materials." In addition, the Examiner rejected claims 27-30 alleging that the claims were indefinite in "the recitation of molecular weight with out giving details of the assay used to ascertain said molecular weight." Applicants contend that these recitations would be understood by one of ordinary skill in the art. Applicants further direct the Examiner's attention to pages 16-17 of the specification, where the interpretation of the immunoelectrophoresis experiments is described.

Without acquiescing in the propriety of this rejection however, and solely to expedite prosecution, applicants have amended the claims to delete the objected-to phrases from the claims. Reference to "bulk antibody" source in claim 27 appears to be not relevant to this claim, since this phrase is not found in claim 27.

Based on the above arguments and amendments, applicants request reconsideration of the pending claims and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

At paragraph 22, the Examiner rejected claims 22 and 30 under 35 U.S.C. § 102(b) as being clearly anticipated by Sullivan

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N.W.
WASHINGTON, DC 20005
1-202-408-4000

et al. Applicants respectfully traverse this rejection, which is now moot as it pertains to claim 22.

It axiomatic that in order for a reference to anticipate the claims under 35 U.S.C. § 102, the reference must contain all aspects of the claim. Sullivan et al. fails to meet this requirement.

The Examiner attempts to support the rejection by alleging that Sullivan et al. "teaches an antivenin composition ... purified from a bulk antibody containing source ...." (Emphasis added). Applicants contend that such is not the case. Sullivan et al. actually teaches an antivenin composition purified from a commercially available source, i.e., commercial antivenin (Crotalidae) polyvalent. Such a commercially available antivenin preparation is not in fact a bulk source.

Contrary to the Examiner's contention, claim 30 is drawn to an unprocessed bulk preparation. The specification states at page 6, lines 9-13, "for example, in the context of antivenin purification, the antibody source may be bulk, unprocessed hyperimmune equine serum, laboratory produced monoclonal antibodies or commercially available antivenins." To more clearly point out and specifically claim the subject matter of the instantly claimed invention, applicants have amended claim 30 to recite "bulk, unprocessed antibody containing source." Therefore, this rejection is overcome and should be withdrawn.

At paragraph 24, the Examiner rejected claims 27-29 under 35 U.S.C. § 103 as allegedly being unpatentable over Sullivan et al. (Proc. West. Pharmacology Soc. 25:188-192 (1982)) in view of

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

Stanworth et al. (Handbook of Exp. Immunology, pages 6.14-6.24, 1978). Applicants respectfully traverse this rejection.

The Court of Appeals for the Federal Circuit has clearly stated that there must be some teaching, suggestion or incentive to support a combination of references such as made in this case. It is the burden of the Patent and Trademark Office to establish a *prima facie* case of obviousness for a § 103 rejection. For example,

> It [the Patent and Trademark Office] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teaching of the references.

In re Fine, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). The Examiner has not met this burden in the instant application.

The Court has further stated in In re Vaeck that simply a motivation or a suggestion to combine the cited art is not sufficient when making a § 103 rejection:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

(Emphasis added). In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). This rejection, based on combination of the applied art, fails both prongs of the test. There is neither a suggestion to combine the applied art, nor a reasonable expectation of success of obtaining the instantly claimed invention even if the references are combined.

Sullivan et al. purportedly teaches isolation and purification of antibodies to rattlesnake venom by affinity chromatography. Sullivan et al., however, neither teaches nor suggests the use of purified F(ab) fragments as an antivenin composition.

The Stanworth et al. publication is entitled "Immunochemical Analysis of Immunoglobulins and Their Sub-Units," and the pages cited by the Examiner appear almost exclusively to pertain to structural relationships and chemical characterization of immunoglobulins. The Examiner, however, has cited page 6.19 which states:

> For example, $F(ab')_2$ fragments from horse antitoxin and horse anti-lymphocyte globulin have been preferred to the whole antibody molecule which may sensitize the recipient to horse Fc determinants.

While there is a reference to antitoxins in the above quote, nowhere is there a suggestion to make a snake antivenin. The term "antitoxin" can refer to any number of antibodies formed in response to antigenic poisonous substances, such as diphtheria, bee stings and bacterial exotoxins. Stedmans Medical Dictionary, 22nd edition, 1972.

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

The Examiner's contention in paragraph 24 of the Office Action, that Stanworth et al. teaches that "the absence of most of the Fc immunogenic determinants has led to the use of $F(ab)_2$ fragments in various clinical contexts," is incorrect. At page 6.14 of Stanworth et al., the document recites that, "[t]reatment of immunoglobulins with proteolytic enzymes found practical use 30 years ago to remove the species-specific antigenic determinants of horse antitetanus antibodies used in passive immunization of humans." (Emphasis added.) Use of "antitetanus antibodies in passive immunization of humans" is clearly distinct from the immunotherapeutic use of antivenins and by no means suggests the use of F(ab) fragments in "various clinical contexts."

At best, Stanworth et al. may suggest the use of $F(ab')_2$ fragments from horse antitoxin and horse antilymphocyte globulin as being preferred to the whole antibody molecule which may sensitize the recipient to Fc determinants (pp. 6.19-6.20). There is no suggestion to combine Stanworth et al. with Sullivan et al. to arrive at the antivenin of the instantly claimed invention. The attempted combination of references fails the first prong of the obviousness test.

Even assuming, *arguendo*, that there was a motivation to combine the applied art (although applicants maintain that such is not the case), there would not have been a reasonable expectation of successfully obtaining the instantly claimed invention. Given that one of skill in the art would have expected that F(ab) fragments might be quickly cleared from the body by the kidney, it would not have been possible to predict that such fragments would

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

prove to be a successful antivenin. Theoretically, the half-life of the F(ab) fragment could have been shorter than that of the venom it was intended to neutralize. If the non-complexed F(ab) was rapidly cleared from the body, it would not bind the venom and thus would not be effective. Alternatively, if the complexed F(ab) fragment and venom could not be cleared from the body because of the size of the complex, it might appear that the antivenin treatment was successful in the short-term. It could still fail in the long-term, since the venom could become uncomplexed, at which time the venom might still be active.

As such, based on the knowledge in the art at the time the application was filed, it could not be predicted in advance that there would be a reasonable expectation of success of obtaining the instantly claimed invention simply by combining information provided in the cited art. Therefore, the combination of references fails both prongs of the test for obviousness, and the rejection of the claims under § 103 should be withdrawn.

The Examiner rejected claims 20, 21, 23-26 under 35 U.S.C. § 103 as being unpatentable over Smith et al. in view of Sullivan et al. and Bernfeld et al. This rejection is moot in light of the cancellation of these claims.

In view of the foregoing amendments and remarks, applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000

37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER

By: Lawrence B. Bugaisky
Lawrence B. Bugaisky
Reg. No. 35,086

Dated: December 16, 1993

LAW OFFICES
FINNEGAN, HENDERSON
FARABOW, GARRETT
& DUNNER
1300 I STREET, N. W.
WASHINGTON, DC 20005
1-202-408-4000